2057-Pos Board B787
Multipoles as Force Field Parameters - Accuracy and Redundancy
Sofie Jakobsen.
Department of Chemistry, Aarhus University, Aarhus C, Denmark.
Simulation of proteins and other large biomolecules rely on a force field representation of the potential energy surface. Fixed charge force fields, like AMBER, CHARMM, OPLS, and GROMOS, are widely used, however, it is well known that they, due to their simplicity provide an inaccurate description of the electrostatic energy component.
In this study, multipoles up to quadrupoles are fitted to reproduce an ab initio electrostatic potential. The accuracy gained by introducing higher order multipoles is significant. However, the inclusion of multipoles as electrostatic parameters is highly associated with additional redundancy among the parameters. In an attempt to resolve redundancy, a large fraction of less important multipoles were identified and eliminated, without affecting the accuracy of the electrostatic potential. Furthermore, it is concluded that the reduced set of chemically important multipoles is transferable to different geometries of the same molecule. This is a promising result with respect to force field development, which highly relies on the assumption of transferability.

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Assessment of Nonpolar Terms in Implicit Solvent Models to Estimate Small Molecule Hydration Free Energies
Martin Brieg[1], Julia Setzler[2], Wolfgang Wenzel[2].
[1]Steinbuch Centre for Computing, Karlsruhe Institute of Technology, Karlsruhe, Germany, [2]Institute of Nanotechnology, Karlsruhe Institute of Technology, Karlsruhe, Germany.
Solvation effects are of great importance to describe many chemical and biological processes, rendering their understanding an important goal of biophysical research. Here we investigate implicit solvent models, which are desired for applications in which an explicit solvent representation is too demanding from a computational perspective. The estimation of hydration free energies for small organic molecules presents a common test case for all solvent models. Unfortunately, a survey of common implicit solvent models showed that their estimates are not as accurate as estimates based on explicit water models, and further improvement of the nonpolar term in these models has been suggested as a possible solution for this problem.[1] We have optimized model parameters for three different nonpolar terms in combination with a generalized Born model to estimate experimental hydration free energies for a large set of small neutral organic molecules. Our results show that a nonpolar term with atom type depended surface tension coefficients delivers the most accurate estimates for a defined set of atom types, yielding a root mean square error of 0.99 kcal/mol and a squared Pearson correlation coefficient of 0.900. For explicit TIP3P water calculations based on the same molecule set, the corresponding values reported by Mobley et al. are 1.26 kcal/mol and 0.888.[2] Our study provides a thorough overview of the capabilities of these three nonpolar terms. We anticipate that the general conclusions drawn from the analysis of our results will help to improve other existing implicit solvent models.
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Size-Modified Poisson-Boltzmann Electrostatics for Realistic Biomolecular Systems
Nuo Wang, Peter Kekenes-Huskey, Shenggao Zhou, Bo Li,
J. Andrew McCammon.
UC San Diego, La Jolla, CA, USA.
Calculating the electrostatic potential (EP) around a biomolecule is essential for many types of biomolecular modeling. When a biomolecule is solvated by an ionic solution, the EP of the system is typically approximated by the solution of the Poisson-Boltzmann equation (PBE). This is a good approximation when the biomolecule is not highly charged. However, the concentrations of counterions can exceed their maximum packing densities near the highly charged regions of the biomolecule as PBE neglects the finite ion radii. A size-modified Poisson-Boltzmann equation (SMPBE) has previously been formulated to integrate ion sizes into PBE to calculate more accurate EP and ion distributions around biomolecules. Here, we extend the implementation of SMPBE to realistic biomolecular systems that contain an arbitrary number of ion species with non-uniform sizes. Specifically, we apply our method to study the Ca^{++} adsorption to the negatively charged cytoplasmic side of the sarcolemma by electrostatic forces. We use an atomic representation of the sarcolemma for the EP calculation and the solution surrounding the sarcolemma contains Ca^{++}, Na^{+}, K^{+} and Cl- ions. Our calculations indicate that, out of all the counterions, Ca^{++} is the most energetically favorable to be adsorbed to the negatively charged lipid head groups. Our results support the so-called Ca^{++} buffering effect by the sarcolemma and explain, from an electrostatics perspective, how the sarcolemma acts as one of the regulating agents of the free Ca^{++} level in the cardiac myocyte cytosol.

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Free-Energy Calculations for Semi-Flexible Macromolecules: Applications to DNA Knotting and Looping
Stefan M. Giovan[1], Robert G. Scharein[2], Andreas Hanke[3],
Stephen D. Levene[4].
[1]Department of Molecular and Cell Biology, University of Texas at Dallas, Richardson, TX, USA, [2]Hypnagogic Software, Vancouver, BC, Canada, [3]Department of Physics and Astronomy, University of Texas at Brownsville, Brownsville, TX, USA, [4]Department of Bioengineering, University of Texas at Dallas, Richardson, TX, USA.
Obtaining accurate values of the conformational free energy of macromolecular systems is one of the most challenging problems in computational chemistry and biology. Systems involving intermediate length scales such as semi-flexible polymer models of circular DNA molecules are particularly intractable, but nonetheless important. We describe an efficient method to obtain highly accurate conformational free energies of biopolymers having arbitrary ratios of contour length L to persistence length P. Our approach is to use thermodynamic integration (TI) to apply internal constraints until the system behaves harmonically and can be analyzed using normal mode analysis (NMA). We apply this method to a discrete semi-flexible harmonic chain model for circular DNA to compute conformational free energies of prime DNA knots up to six irreducible crossings and an unknotted DNA circle containing a pair of looped domains. We discovered an unanticipated bifurcation transition in the looping free energy as a function of DNA size. This entropy-driven transition is of particular relevance for target-site selection by proteins that bind to multiple DNA sites separated by large linear distances along the genome. Such scenarios arise naturally in mechanisms of gene regulation and the action of type-II topoisomerases. Our procedure is completely general and applicable to multiscale models of any macromolecular system including proteins or other complex polymers.

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Free Energy Calculation of Protein Conformational Changes using Parallel Cascade Selection Molecular Dynamics Simulation and Markov State Model
Yasutaka Nishihara[1], Ryuhei Harada[2], Akio Kitao[1].
[1]University of Tokyo, Tokyo, Japan, [2]RIKEN, Hyogo, Japan.
Free energy calculation of conformational changes of macromolecules by Molecular Dynamics (MD) simulations often require long time simulations and the analysis of large amounts of simulation data. To accelerate conformational changes and enhance sampling efficiency, many methodologies have been proposed, for instance, steered MD, replica exchange, metadynamics and umbrella sampling. In these methods, optimal parameters such as biasing forces and constraints need to be adjusted for interests.
In this study, we provided an efficient free energy calculation method based on Parallel Cascade Selection MD (PaCS-MD) and Markov State Model (MSM). PaCS-MD is used to generate conformational transition pathway under the condition that a set of reactant and product structures is known a prior. In PaCS-MD, the cycle of short multiple independent MD simulations and the selection of the structures close to the product structure for the next cycle are carried out iteratively until the simulated structures move sufficiently close to the product structure. MSM is used for the studies of folding and conformational changes of macromolecules by MD simulations. In MSM, the configuration space is discretized into microstates, and a transition matrix describing the transition probabilities between microstates is calculated from the simulation data. The free energies can be calculated from the stationary probabilities, which were computed from PaCS-MD trajectories by using MSM.
MSM requires the dynamics of the system only to be Markovian, and no further assumption on the system distribution. This is a significant advantage for analyzing simulation data. To estimate our method, we calculated free energy profiles of folding of mini-proteins and large conformational changes of proteins, for example chignolin, T4-Lysozyme and actin.

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A Computational Method Including Protein Flexibility to Estimate Affinities with Small Ligands
Ariane Nunes-Alves, Guilherme M. Arantes.
Instituto de Química - Universidade de São Paulo, São Paulo, Brazil.
Computational methods are used to generate protein-ligand complex structures and predict their binding affinities. Usually protein flexibility is not fully